IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ales Franc
Application No.	:	10/549,296
Filing Date	:	September 15, 2005
For	:	PHARMACEUTICAL COMPOSITION CONTAINING PLATINUM COMPLEX AS ACTIVE SUBSTANCE AND METHOD OF MANUFACTURING THEREOF
Examiner	:	Shirley V. Gembeh
Art Unit	:	1618
Confirm. No.	:	1964

5 Pages
Via EFS
Attn: Examiner Gembeh
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. 1.132

Dear Examiner Gembeh:

1. I, the undersigned, Petr Sova, PharmDr., Ph.D. do hereby declare:

2. I am skilled in the field of the subject application. Specifically, I have worked for 15 years in the field of research and development of original and generic drugs in the following capacities: scientific research worker, head of research project, project director for proprietary anticancer drugs. I hold the following academic degrees: M.Pharm. degree in Pharmacy (Charles University Prague, Faculty of Pharmacy, Hradec Králové); Certificate

level I in Pharmaceutical technology (Institute for Postgraduate Medical Education Prague); Ph.D. degree in Pharmaceutical Technology (Charles University Prague, Faculty of Pharmacy, Hradec Králové); and PharmDr. degree in Pharmacy (Charles University Prague, Faculty of Pharmacy, Hradec Králové).

3. I understand the English language have read both the above-identified application and U.S. Patent No. 6,136,336 to Tanaka, et al. ("Tanaka, et al.")

4. I have completed the study summarized below to determine the compatibility of (*OC*-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum(IV), which is the compound of formula (II) ("LA-12") according to above-identified application with selected excipients. The compatibility of LA-12 with the excipients was then compared with the compatibility of (*OC*-6-43)-bis(acetato)amminedichloro(cyclohexylamine)platinum(IV) ("JM216") with the excipients. The study was implemented under the following conditions and produced the following results:

Abbreviations:

LA-12: (*OC*-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum(IV)

CAS No.: [250611-20-2]

JM216: (*OC*-6-43)-bis(acetato)amminedichloro(cyclohexylamine)platinum(IV)

RH: Relative humidity

Introduction:

The objective of this study was to select the most suitable/compatible excipients for

further development of stable, safe and effective pharmaceutical formulations. Liquid chromatography was employed for the determination of LA-12 content and chromatographic purity.

Physicochemical specification of LA-12:

TESTED PARAMETERS	LIMITS
Appearance	Light yellow powder
Identity	
-HPLC	Identical with RS
-IR-spectrometry	Identical with RS
Active substance content (HPLC)	(98.0 - 102.0) %
Chromatographic purity (HPLC)	
-($PtCl_3$(ac)(am)(NH_3))	Max. 0.5 %
-Individual unknown impurity	Max. 0.1 %
-Sum of unknown impurities	Max. 0.5 %
-Sum of all impurities	Max. 1.0 %
Loss on drying TGA	Max. 6.0 %
Residual solvents - acetone	Max. 0.5 %

Compatibility of LA-12 with selected excipients:

The chemical compatibility studies of LA-12 with some excipients using HPLC analysis were performed. LA-12 was mixed with each individual excipient. Samples were stored at 40°C/75% RH for three months or were sealed stored at 50°C for three weeks. The results of HPLC analysis are presented in Tables 1 and 2, which suggest potential interaction between the drug and the excipients used.

Table 1

Storage at 40°C/75% RH		3rd Month
LA-12+glycerolgelatine mass	LA-12 content	101.40 %

Table 2

Storage at 50°C		3rd Week
PEG 400	LA-12 content	3.97 %
Propylen Glycol Laurate	LA-12 content	16.48 %
Lauroyl Macrogolglycerides (Polyoxylglycerides)	LA-12 content	1.65 %
Polyglycerol oleate	LA-12 content	1.96 %
Polysorbate 80 (PEG-20 Sorbitan Oleate)	LA-12 content	7.05 %

Conclusions:

In view of the fact that Tanaka et al. teaches polyethylene glycol (PEG) to be the most appropriate suppository base for JM216 and taking into account the fact that JM216 and LA-12 have similar chemical structures, it would be expected that PEG could be a suitable main ingredient for formulating LA-12, as well. However, at variance with this expectation, the study surprisingly showed high instability of LA-12 in the presence of PEG.

This substantially unexpected finding means that LA-12 is far more sensitive to one of the usual excipients than is JM216. This, in turn, means that if JM216 is compatible with some excipient(s), then LA-12 need not be *a priori* compatible with identical excipient(s). If LA-12 is really compatible with the ingredient(s) with which JM216 also is compatible, then such compatibility of LA-12 should not be considered as predictable based simply on the ground that LA-12 has similar a chemical structure as JM216.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: October 20, 2009